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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,743	ALLEY ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,11,13,34-39,43,64,65,74 and 76-112* is/are pending in the application.

4a) Of the above claim(s) *10,11,13 and 76-112* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-39, 43, 64-65 and 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/25/08; 8/13/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 10-11, 13, 34-39, 43, 64-65, 74 and 76-112 are pending.

2. Applicant's election with traverse of Group II, Claims 34-39, 43, 45-47, 50-54, 58, 62-65, and 73-75 (now claims 34-39, 43, 64-65 and 74) drawn to a method of reducing and conjugating a drug to an antibody, filed September 14, 2009, is acknowledged.

The traversal is on the grounds that although applicants do not agree with the holding of lack of unity, applicants hereby elect Group II.

Applicants' traversal has been fully considered but is not deemed persuasive for reasons of record.

Therefore, the restriction requirement is still deemed proper and is therefore made FINAL.

3. Claims 10, 11, 13 and 76-112 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 34-39, 43, 64-65 and 74, drawn to a method of reducing and conjugating a drug to an antibody, are being acted upon in this Office Action.

5. Claim 37 is objected to because it is unclear the abbreviation "AEB", "AEVB", MMAF", MMAE" and "AFP" stand for. While abbreviation can be used in a claim, to avoid potential confusion, the first recitation of the abbreviation should be preceded by the full terminology, such as auristatin E with paraacetyl benzoic acid (AEB), for example.

6. The International Search Report and Written Opinion on the information disclosure statements (IDS), filed August 25, 2008 have been considered but crossed out because said Search Report and Written Opinion are not appropriate to be printed on an issued patent.

7. The disclosure is objected to because of the following informality: the font in paragraphs [0109], [0110], [0111], [0112] and [0113] needs to be corrected.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 34-39, 43, 64-65 and 74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of reducing or conjugating any drug to any antibody comprising fully reducing any antibody reducing agent, and then treating the fully reduced antibody with limiting amounts of any redoxidizing agent as set forth in claim 34, (2) a method of producing any antibody with selective conjugation of any drug comprising fully reducing any antibody for a period of time sufficient to produce interchain thiols, as determined by DTNB titration, by adding a large excess of any reducing agent and incubating the solution at about 37 °C for about 30 minutes, purifying the antibody, partially reoxidizing the antibody using any oxidizing agent to form at least one interchain disulfide bond by cooling the reduced antibody to 0 °C; treating the reduced and cooled antibody with 1.5 to 2.5 molar equivalents of any oxidizing agent as set forth in claim 64-65 and (3) a method of preparing any conjugate of any protein having one or more disulfide bonds and any drug, comprising fully reducing any protein with any reducing agent; partially reoxidizing the protein with any reoxidizing agent; and conjugating the drug reactive with free thiols to the protein as set forth in claim 74.

The claim 34 encompasses a method of preparing any conjugate comprising any antibody and any drug using any reducing agent and partially reoxidizing the antibody with any oxidizing agent under any condition.

The claim 64 encompasses a method of producing any antibody with selective conjugation of any drug comprising fully reducing any antibody for a period of time sufficient to produce interchain thiols, as determined by DTNB titration, by adding a large excess of any reducing agent and incubating the solution at about 37 C for about 30 minutes; and then reoxidizing the antibody with any oxidizing agent under any condition.

The claim 74 encompasses a method of preparing any conjugate comprising any protein and any drug using any reducing agent and partially reoxidizing the protein with any reoxidizing agent.

The scope of the each genus includes many members with widely differing structural, chemical, and physiochemical properties such as widely differing nucleotide sequences, and biological functions. Furthermore, each genus of protein, antibody and/or drug is highly variable. A significant number of structural and biological differences between genus members exist. There is no information regarding what structural features would likely be associated with such protein, drug and antibody in the conjugate for the claimed method. Further, there is insufficient disclosure as to the binding specificity associated with the CDRs structure of such antibody for the claimed method.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., complete or partial structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, method of making the claimed invention, level of skill and knowledge in the art and predictability in the art sufficient to show that applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

The specification describes a method of preparing a conjugated antibody comprising just cAC10 antibody that binds to CD30 conjugated to just vcMMAE wherein the method comprises the steps of (a) adding excessive amount of a reducing agent DTT or TCEP to a solution

comprising antibody cAC10 that binds to CD30 in 0.025 M sodium borate, pH 8, 0.025 M NaCl, 1 mM DTPA for two hours at 37 °C to fully reducing the antibody for a period of time to sufficiently to produce interchain thiols as determined by DTNB titration, (b) purifying the antibody, (c) partially reoxidizing the fully reduced antibody by adding an oxidizing agent 5,5'-dithiol-bis-2-nitrobenzoic acid (DTNB) to form cAC10 conjugated to vcMMAE and (d) purifying the vcMMAE conjugated antibody, see pages 54-58.

At the time of filing, applicants are not in possession of a method of preparing a conjugate of any protein, any protein such as any antibody having one or more disulfide bonds and any drug, using any reducing agent; and reoxidizing the undisclosed protein or drug or antibody with any oxidizing agent. In particular, the conditions to which the condition and reagents use for the claimed method are not adequately described.

The specification does not describe the complete structure of any conjugate comprising any protein other than the cAC10 antibody that binds to CD30 conjugated to just vcMMAE using just reducing agent DTT or TCEP and oxidizing agent DNTB.

While general knowledge in the art may have allowed one skill in the art to conjugate antibody to a drug, there is no census in the art about conjugating antibody to a drug could apply to conjugating any protein to any drug using any reducing agent and any oxidizing agent for the claimed method and still maintain structure and function.

Because the described method of conjugating just cAC10 antibody that binds to CD30 to vcMMAE using excessive reducing dithiorethol (DTT) or TCEP to fully reduce said cAC10 antibody and reoxidized said antibody using DTNB is not representative of the entire claimed genus, one of skill in the art would conclude that applicant was not in procession of the claimed genus as a whole at the time of filing. Therefore, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims 34-39, 43, 64-65 and 74.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Further, possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115). Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 and revision of the Written Description Training materials, posed April 11, 2008 http://www.USPTO.gov/web/menu/written.pdf.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claim 64 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 64 is indefinite because it is unclear as to what reducing agent is being added to which solution at about 37°C for 30 minutes. Further, the order in which the titration DTNB before the step of reducing the antibody is improper.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 34-39, 64-65 and 74 are rejected under 35 U.S.C. 102(a) as being anticipated by Francisco et al (Blood 102(4): 1458-1465, August 2003, PTO 1449) as evidenced by Sears et al (Proc Natl Sci USA 72(1): 353-357, January 1975; PTO 892).

Francisco et al teach a method of preparing a protein conjugate such as antibody conjugate to a drug such as cAC10-vcMMAE wherein the antibody is cAC10 that binds to CD30 having one or more disulfide bonds and the drug is monomethyl aruistatin E (MMAE), see entire document, page 1459, right col. Conjugate preparation, in particular. The reference method comprises the step of reducing the antibody with excess molar amount of reducing agent such as dithiothreitol (DTT), incubating such solution at 37°C for 30 minutes, purifying the antibody

through Sephadex G-25 resin chromatography, the amount of interchain thiol concentration was determined by reaction with DTNB (5,5'-dithiobis(2-nitrobenzoic acid), partially reoxidizing the antibody using an oxidizing agent to form at least one interchain disulfide bonds by cooling the reduced antibody on ice and then treating the reduced and cooled antibody with DTNB with a 2.5 mg/ml (molar), and purify the drug/antibody conjugate using size-exclusion chromatography (see page 1459, right col., paragraph conjugate preparation). The reference antibody is fully reduced sine the drug/antibody ratio of cAC10-vcMMAE is 8:1 as evidenced at page 24 paragraph [0089] of instant specification. Evidentiary reference Sears et al teaches reoxidation of human IgG1 with its four interchain disulfide bond to form H2L2 after reduction of all interchain disulfide bonds by simply exposed to air and adjust pH with Tris buffer at 0.1M NaCl, 1mM acetate at pH 7.5, ionic strength of 0.14 (see page 353, left col., Reduction and Reoxidation, right col., in particular). Thus, the reference teachings anticipate the claimed invention.

14. Claims 34-39 and 74 are rejected under 35 U.S.C. 102(a) as being anticipated by Doronina et al (Nature Biotechnology 21(7): 778-941, July 2003, PTO 892) as evidenced by Sears et al (Proc Nat Acad USA 72(1): 353-357, January 1975, PTO 892).

Doronina et al teach a method of preparing a protein conjugate such as antibody conjugate to a drug wherein the antibody is cAC10 that binds to CD30 or cBR96 antibody that binds to Lewis Y antigen wherein the antibody having 8 disulfide bonds and the drug is auristatin or monomethyl aruistatin E (MMAE), see entire document, page 783, left col. Conjugate preparation, in particular. The reference method comprises the step of reducing the antibody with excess molar amount of reducing agent such as 10 mM of dithiothreitol (DTT), incubating such solution at 37°C for 30 minutes, purifying the antibody through Sephadex G-25 resin chromatography, the amount of interchain thiol concentration was determined by reaction with DTNB (5,5'-dithiobis(2-nitrobenzoic acid). This reductive conjugation method preserves mAb affinity and is applicable to a high degree of conjugate uniformity and proceeds with yields in the rang of 80% based on the mAb component, see page 779, right col. 1, first paragraph, in particular. Evidentiary reference Sears et al teaches reoxidation of human IgG1 with its four interchain disulfide bond to form H2L2 after reduction of all interchain disulfide bonds by simply exposed to air and adjust pH with Tris buffer at 0.1M NaCl, 1mM acetate at pH 7.5, ionic strength of 0.14 (see page 353, left col., Reduction and Reoxidation, right col., in particular). Thus, the reference teachings anticipate the claimed invention.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
December 18, 2009